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Craniofacial Anthropometric Analysis in Several Types of Chondrodysplasia

Alasdair G.W. Hunter

Division of Genetics, Children's Hospital of Eastern Ontario, and Department of Pediatrics, University of Ottawa, Ontario, Canada

Craniofacial anthropometric analysis is a generally accessible technique that potentially offers an objective tool to reduce the subjectivity of syndrome diagnosis and to aid in differential diagnosis. The chondrodysplasias might seem an unlikely target for this technique in that they mainly cause disproportionate growth and are subject to radiographic diagnoses. However, the diagnosis of skeletal dysplasias remains challenged by subjectivity of radiologic assessment, and specific radiologic signs may appear only with age or may no longer be present at the time of examination. Thus patients continue to defy diagnosis, have their diagnosis changed, and/or be misdiagnosed, even in specialized centers.

Certain chondrodysplasias have obvious craniofacial involvement while others appear to share a specific gestalt. This paper reports craniofacial anthropometric analysis for several of the more common chondrodysplasias and confirms that some do display a characteristic pattern that is in keeping with what might be expected. Furthermore, the concurrent assessment of several different conditions by a single observer has emphasized the importance of considering the possibility of systematic measurement error in any such studies.

KEY WORDS: anthropometrics, achondroplasia, hypochondroplasia, diastrophic dysplasia, pseudoachondroplasia, spondyloepiphyseal dysplasia congenita, chondrodysplasia, measurement error

INTRODUCTION

The major visible impact of the chondrodysplasias is on growth and body proportions. While the diagnosis of these conditions generally rests upon their radiographic signs, the facial gestalt may often provide an important first impression as to the diagnosis. This is well recognized for certain conditions such as achondroplasia, where the craniofacial changes may be quite marked, but there is some consensus that several other bone dysplasias may include more subtle alterations in facial appearance. Furthermore, in very young children or adults with mature bones the diagnostic radiographic findings may not be apparent and the facial findings might provide an important aid to diagnosis.

However, diagnosis by the clinical assessment of facial appearance is generally subjective and may be biased. Attempts to develop a more objective approach have included two dimensional [Farkas et al., 1980] and three dimensional [Thomas et al., 1989] photogrammetry, radiographic cephalometry [Pruznansky, 1977; Kreiborg, 1985], and anthropometric pattern analysis [Farkas et al., 1985a,b]. Anthropometry involves the direct measurement of surface distances and arcs and its use in craniofacial assessment has successfully been applied to establish a pattern profile of "Z" scores in several syndromes [Niebuhr, 1979; Farkas et al., 1985a,b; Kolar et al., 1985; Ward and Bixler, 1987; Allanson et al., 1993].

Craniofacial anthropometric measurements and pattern profile analysis were carried out as part of a broader study of individuals with a variety of chondrodysplasias. The objectives were to document which measurements differed from the average population in syndromes with acknowledged craniofacial involvement, and to assess whether some conditions where the face is generally accepted as uninvolved might show some changes of potential diagnostic usefulness. This paper presents the results in achondroplasia, hypochondroplasia, pseudoachondroplasia, spondyloepiphyseal dysplasia congenita, diastrophic dysplasia, and multiple epiphyseal dysplasia. Several other conditions were studied but in insufficient numbers for analysis.

MATERIALS AND METHODS

Craniofacial anthropometric measurements were carried out on 226 individuals who had a non-lethal

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Address reprint requests to Dr. Alasdair Hunter, Division of Genetics, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa ON, Canada, K1H 8L1.

chondrodysplasia. Table I provides a breakdown by diagnosis and age group. There were 101 females and 96 males in the groups reported in this paper. Measurements were carried out in Ottawa ON, Wilmington DE, Melbourne VIC, Sydney NSW, Manchester and Cardiff UK. With the exception of one East Indian woman and one Arabic boy, both with achondroplasia, the patients were of mixed European caucasian ancestry. Patients were first contacted in writing by their own genetic department in order to obtain permission for AGWH to communicate with them and explain the nature of the project. A small minority of individuals were introduced at regular clinics or volunteered at the 1994 American or Ontario Little People's Association conventions. The study was approved by the Research Ethics Review Committee of the Children's Hospital of Eastern Ontario. It was also subject to ethics review in Sydney and Cardiff.

A total of 21 craniofacial measurements per patient were performed by the author from the standard landmarks shown in Fig. 1, using an non-elastic tape (T), Spreading (P), and sliding (S) callipers, and with the subject and researcher seated. An additional nine measurements aimed at assessing growth and body proportions were also carried out but are not reported here.

The values obtained were then entered into SPSS/PC+ and the computed differences from the age and sex appropriate mean [Farkas, 1994] (see discussion of ft-ft in Discussion) were divided by the standard deviation to give a Z-score. The group mean Z-scores were plotted to produce a craniofacial profile. This paper represents an analysis of the six conditions where approximately 20 cases or more have been studied. Pattern variability was assessed by calculating σ_z [Garn et al., 1984a] for the mean Z-score pattern, and intergroup comparisons by using the correlation coeficient r_z of the paired Z-scores of the two pattern profiles [Garn et al., 1984b].

RESULTS

Measurement Error

As a first step in analysis the mean pattern profiles of each of the six chondrodysplasias were compared to look for systematic measurement error as evidenced by a consistent deviation from the mean of one or more Z-scores across the disparate syndromes, especially if it was also seen in mild multiple epiphyseal dysplasia (MMED). The latter patients were included primarily as a control group who had joint pain, but normal stature and appearance. All six chondrodysplasias had an ft-ft >2 SD above the mean and, as seen in Figure 2, the mandibular and maxillary arcs in achondroplasia (ACH) were unexpectedly normal, while go-go, t-sn-t and t-gn-t were relatively increased in MMED. This evidence of a systematic measurement error was supported when a pattern consistent with the MMED patients was obtained subsequently on a sample of 20 unaffected adult volunteers (data not shown). Given the consistency of this measurement error, the Z-scores from the ACH, hypochondroplasia (HYPO), pseudoachondroplasia (PACH), diastrophic dysplasia (DD), and spondyloepiphyseal dysplasia congenita (SEDC) patients in the study were corrected by subtracting the Z-scores of the average stature and appearing MMED patients, and then replotted to give their pattern profile.

Achondroplasia

Figure 3 shows the resultant plot for achondroplasia which can be compared with that of Figure 2. A number of measurements show important deviation from the population average and the pattern variability (σ_z) was 1.52. The skull base (t-t) is somewhat narrow (−1 SD), while the OFC is increased (+1.5 SD), primarily due to an increased width (eu-eu, +2.64 SD) rather than length (g-op, +0.12 SD). The facial depths (t-n, t-sn, t-gn), especially that of the mid-face (t-sn), are confirmed to be shallow, and are in keeping with reduced maxillary (t-sn-t), and to a lesser extent mandibular (t-gn-t) arcs which are now apparent in the corrected plot. Finally there is significant shortness of the nose in achondroplasia (n-sn −2.75 SD), while the increased inner and slightly elevated outer-canthal distances support the relatively frequent observation of telecanthus and occasional occurrence of true ocular hypertelorism in achondroplasia.

The relatively large number of individuals with achondroplasia permitted analysis by age group. Figure 4 shows the Z-score pattern profiles across four separate age categories (0–4 years, 4 cases; >4–9 years, 20 cases; >9–16 years, 17 cases, >16 years, 48 cases). The correlation coefficient (r_z) of the pattern is high between the groups, even with the small number in the youngest age category (r_z: Age 0–4 years with >4–9 years = 0.91; with >9–16 years = 0.85; with >16 years = 0.79; Age >4–9 years with >9–16 years = 0.95; with >16 years = 0.91; Age >9–16 years with >16 years = 0.96. All P values <0.0001). This suggests that any random

TABLE I. Numbers of Cases by Diagnosis and Age Group

	Age groups				
Diagnosis	<4 Years	>4–<9 Years	>9–<16 Years	>16 Years	Total
Achondroplasia	4	20	17	48	89
Hypochondroplasia	1	2	10	12	25
Diastrophic dysplasia	1	5	2	9	17
Mult. epiphyseal dysplasia	0	2	9	12	24
Pseudoachondroplasia	0	2	5	14	21
Spondyloepiphyseal dysplasia	1	2	4	14	21
Other[a]	0	2	9	18	29

[a]Eight other specific chondrodysplasias are included in this group but none occur with sufficient frequency to allow analysis.

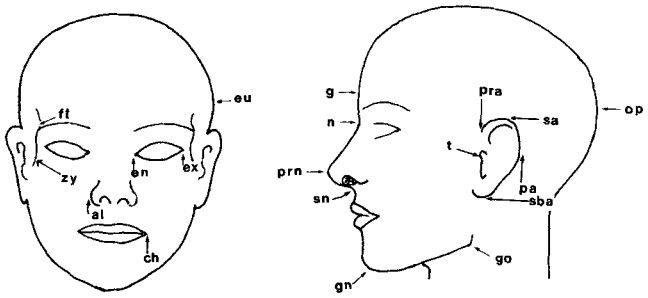

Fig. 1. Cartoon of face showing landmarks used for craniofacial measurements. Head Width eu-eu (P); Skull Base Width t-t (P); Mid Frontal Distance ft-ft (P); Upper Facial Width zy-zy (P); Lower Facial Width go-go (P); Head Length g-op (P); Upper Facial Depth t-n (P); Mid Facial Depth t-sn (P); Lower Facial Depth t-gn (P); Nasal Protrusion sn-prn (S); Total Facial Height n-gn (S); Nose Height n-sn (S); Nasal Width al-al (S); Mouth Width ch-ch (S); Inner Canthal Dist en-en (S); Outer Canthal Dist ex-ex (S); Ear Width pra-pa (S); Ear Length sa-sba (S); Maxillary Arc t-sn-t (T); Mandibular Arc t-gn-t (T); Head Circumference OFC (T).

measurement error has not been significant enough to obscure a pattern profile which is intrinsic to the condition.

Hypochondroplasia

The pattern profile of hypochondroplasia is included in Figure 3 and allows a comparison with achondroplasia. The pattern is a striking parallel, but with a milder expression of the changes which are more prominent in achondroplasia. The correlation coeficient (r_z) between the two patterns was 0.87, while the σ_z was only 0.35 for hypochondroplasia. There is no trend of any measurement in a direction different from that seen in achondroplasia.

Pseudoachondroplasia

Although the number of observations is limited (21), there does not appear to be any marked pattern profile in pseudoachondroplasia (Fig. 5) and the variability index was the lowest of the conditions studied (0.18). There is a slight trend towards brachycephaly (g-op −0.93 SD, eu-eu + 0.3 SD) and an expected accompanying minimal decline in OFC (−0.7 SD).

Diastrophic Dysplasia

Again with limited observations (17), there appears a trend to relative brachycephaly (g-op −1.1 SD, eu-eu +0.67, OFC −0.69) (Fig. 5). The ft-ft is narrower than in the other conditions studied and the lower facial depth (t-gn −1.04 SD), mandibular (t-gn-t −1.11 SD) and maxillary (t-sn-t −0.79 SD) arcs were somewhat reduced. The patients showed a trend towards a wide nose (al-al + 1.79 SD), telecanthus (en-en +1.3 SD), and somewhat short ear (sa-sba − 1.08 SD). The variability index was 0.62.

SEDC

The most striking finding in SEDC (Fig. 6) is the overall trend to reduced Z-scores with all but nose and mouth width falling at or below the means. This suggests a reduction in craniofacial size with the maximum changes in the mid and lower face (t-sn −0.73 SD; t-sn-t −1.4 SD; t-gn −1.38 SD; t-gn-t −1.8 SD). The reduction in the mandibular region is greater than that in the maxillary. The overall variability index was 0.34.

DISCUSSION

Craniofacial anthropometry has been advocated as a potentially useful research and diagnostic tool in dys-

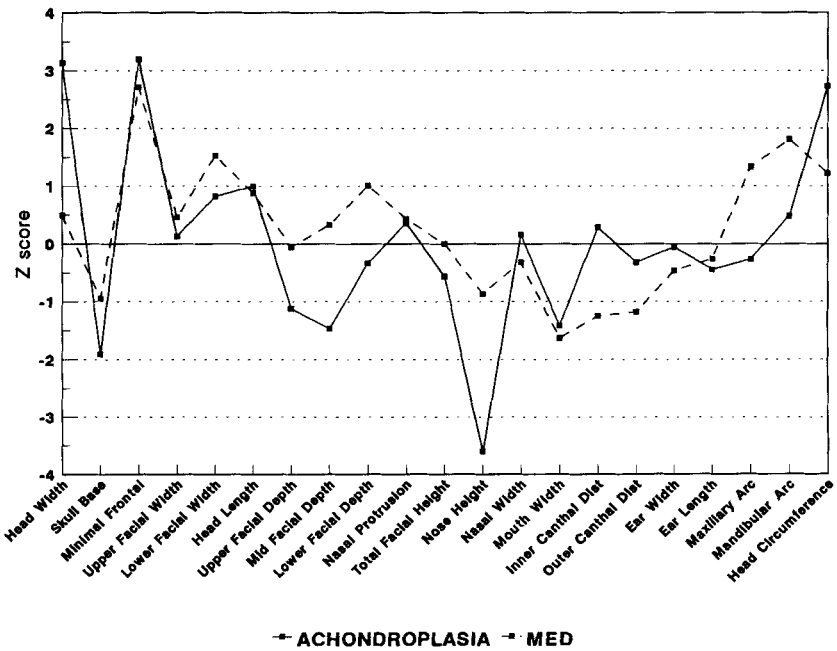

Fig. 2. A comparison of the craniofacial pattern profiles in achondroplasia and mild multiple epiphyseal dysplasia using uncorrected data.

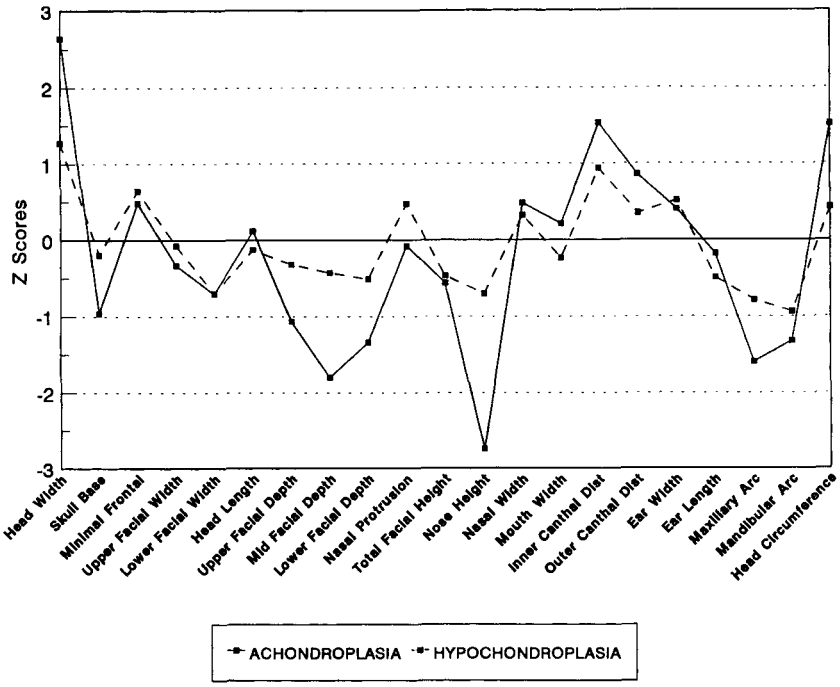

Fig. 3. A comparison of the craniofacial pattern profiles in hypochondroplasia and achondroplasia, after correction for systematic measurement error.

morphology because it is non-invasive, requires minimal time and inexpensive equipment, is technically simple, and there are population data with which to compare results [Ward, 1989; Ward and Jamison, 1991]. Once data are obtained, they may be manipulated in different ways depending upon the interests of the investigator.

The dysmorphologist is most often concerned with a comparison between two syndromes, or that of an individual against one or more syndromes, and conversion

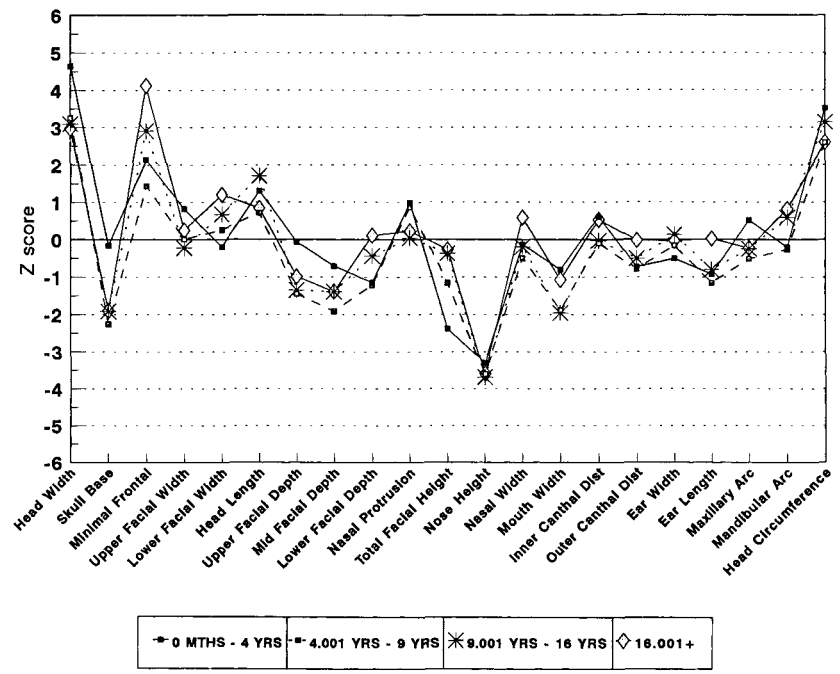

Fig. 4. Craniofacial pattern profiles of achondroplasia by age groups using data uncorrected for systematic measurement error.

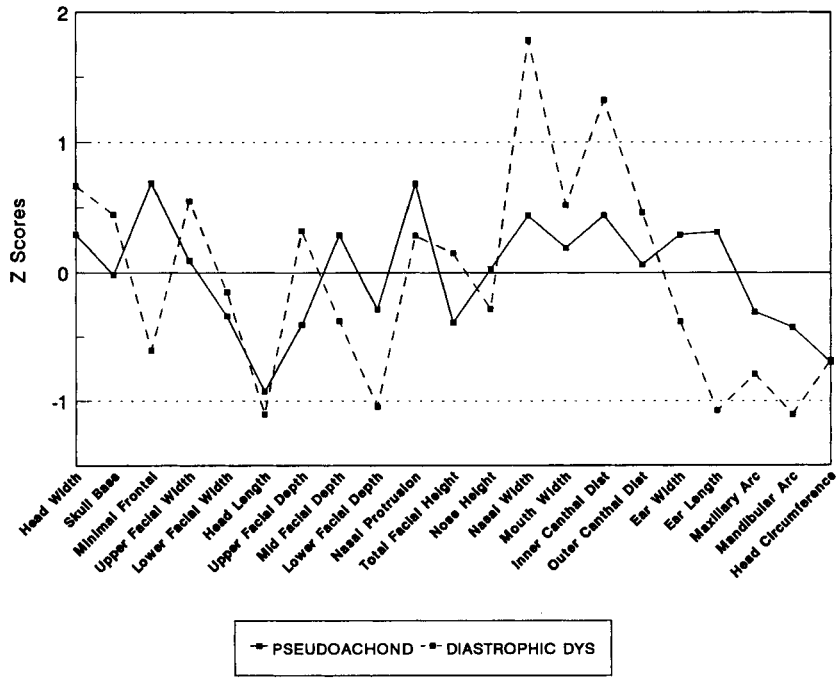

Fig. 5. The craniofacial pattern profiles in pseudoachondroplasia and diastrophic dysplasia after correction for systematic measurement error.

of the data to normalized Z-scores with statistical and graphical study of the pattern profile has strong appeal. This approach makes allowance for the age related differential growth of certain facial distances and immediately highlights measurements that deviate from the population or syndrome mean. In contrast, a craniofacial team, with an eye to possible surgical repair, may be more interested in the age specific proportions of one measurement to the next. The normal age related indices for a wide range of such comparisons have been reported [Farkas and Munro, 1987]. A hypothetical example of a wide nose (al-al) in a wide face (zy-zy) can il-

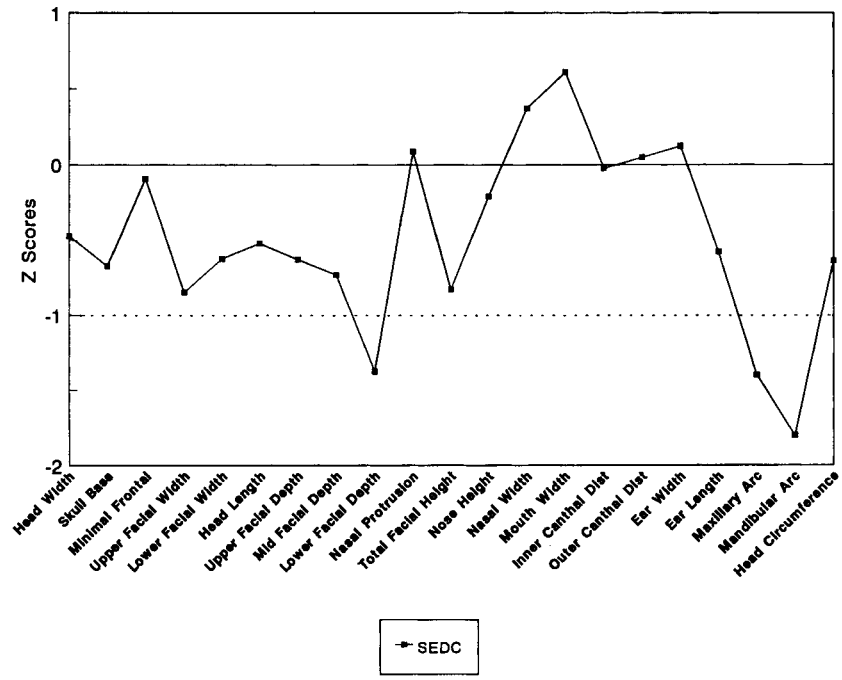

Fig. 6. The craniofacial pattern profile in spondyloepiphyseal dysplasia congenita corrected for systematic measurement error.

lustrate the differing perspectives. Those measurements may provide a satisfactory (normal) nose-face index (al-al × 100/zy-zy). Similarly, an increase in one measure or a decrease in the other may cause the same change in the index. However, the dysmorphologist would be more interested to know that a syndrome is characterized by a wide nose and by a wide face, or a change of a value in a specific direction. This paper has been written from the perspective of the clinical geneticist and did not consider proportional indices.

This study supports the existence of facial involvement in several of the chondrodysplasias and has allowed the nature of the changes to be more specifically *identified.* The pattern variability in achondroplasia is large, and the skull measurements are those that would be expected in the presence of true macrocephaly and a contracted skull base. Those of the face confirm a mid-facial hypoplasia, short nose and tendency towards telecanthus (+/− hypertelorism). The graphical and statistical age comparisons suggest that these manifestations are present early and do not change greatly with age. However, longitudinal measurements on individual patients and more studies on young children would be of interest. The shape of the face and relative proportions of different measurements change with age [Farkas and Monro, 1987], and thus the fact that the achondroplasia pattern is present across the age groups suggests that the the underlying growth asymmetry of the face is maintained.

When this study began, the gene for achondroplasia had not been identified [Shiang et al., 1994], and that for hypochondroplasia had not been mapped to the same region of 4p [Le Merrer et al., 1994]. There was no consensus that these were two distinct conditions. Leri and Linossier [1924] described hypochondroplasia as a mild variant of achondroplasia. The paper of Walker et al. [1971] stated that ACH "shows a uniform clinical and roentgenographic picture," and agreed with Silverman [1968] that mild or incomplete forms of ACH do not occur. This led to general acceptance that hypochondroplasia was distinct from achondroplasia. The two conditions were not observed within the same family, and radiologic criteria for the diagnosis of HYPO were developed [Frydman et al., 1974; Hall and Spranger, 1979]. The latter authors found no parallel between the metacarpophalangeal profile in ACH and HYPO. However, they did note that a significant proportion of patients with HYPO (56%) had macrocrania, and that the diagnosis of HYPO was often one of exclusion. McKusick et al. [1973] considered that ACH and HYPO were distinct but allelic. Oberklaid et al. [1979] questioned the diagnosis of HYPO in the mother in the family of McKusick et al. [1973], and stated that there was overlap in all the manifestations except the face, whose ratio of size to that of the skull was the basis for the distinction, which they termed "arbitrary." Wynne-Davies et al. [1981] expressed the view that severe HYPO is indistinguishable from mild ACH.

The view that ACH and HYPO are not the result of variable expression of the same mutation within and between families has been confirmed by the finding of codon-specific mutations in the FGFR3 gene in patients with confirmed achondroplasia [Bellus et al., 1995a; Superti-Furga et al., 1995]. Different mutations have been found in hypochondroplasia [Bellus et al., 1995b]. It is puzzling that the least severe allele (HYPO) is associated with mental retardation while ACH is not.

During the study I was struck by the marked variation of the facial involvement in achondroplasia and this, together with the overlap in stature and associated clinical findings with HYPO, led to an interest in comparing the two craniofacial profiles. The two patterns are visually similar (Fig. 3) and highly correlated (r_z = 0.87), with HYPO showing findings consistent with a "milder expression of ACH." Specifically there is a slight increase in OFC due to a widened eu-eu, and also a trend to underdeveloped facial depths, lengths, and arcs which, however, is much less marked than in ACH. Thus at the overlap of clinical expression molecular studies may be required to distinguish ACH and HYPO.

Only three of the seventeen patients with diastrophic dysplasia had been born with a cleft palate but the pattern profile showed a relatively small lower face consistent with a trend towards the "Pierre-Robin" sequence. The tendency to a broad nose and telecanthus substantiated the subjective impression often noted at the time of mensuration. The relatively short ears are likely the result of post-inflammatory scarring.

The relatively small mandible in SEDC was predictable, but the overall reduction in craniofacial size was unexpected. In almost all patients the diagnosis of SEDC was based upon clinical history, examination and radiographic confirmation. In a few the clinical history and findings were compatible but early radiographs had not been available for review. Inclusion of an occasional misdiagnosed patient would tend to obscure rather than create a specific pattern profile. Six of the twenty-one patients with SEDC had been born with a cleft palate.

The pattern profile in pseudoachondroplasia was unremarkable and showed the least variability among the conditions studied. Some individuals with pseudoachondroplasia have commented that they believe the nose to be particularly well developed in that condition. However, the nasal measurements were all well within the normal range and the observation may relate more to visual comparison with certain other chondrodysplasias.

Anthropometry relies on soft tissue landmarks and may be subject to both random and systematic measurement error [Ward, 1989; Ward and Jamison, 1991]. Problems inherent to some of the smaller measurements, inadequate training, and poor technique may lead to problems of intra-observer precision and inter-observer repeatability. As recommended by Ward [1989], the measurements used in this study were selected to represent all the major dimensions of the face and to avoid some of the smaller measures most subject to error [Allanson et al., 1993].

Lack of precision leads to random error and may obscure the presence of a pattern profile, or possibly, in cases where a small number of cases are studied, result in a spurious pattern profile. Measurements for this

study were usually carried out in the home in concert with a standard physical examination and interview. This situation was not conducive to a systematic assessment of precision. However, the similarity of the pattern seen across the four age groups in achondroplasia, even for those under 4 years where only four subjects were studied, supports reasonable precision.

A systematic error may occur because of differences in technique, instrumentation, or because the control and study population are not truly comparable, for example, in ethnic mix. The former may include variations in the identification of landmarks or the reading of instrument scales. Ward [1989] has recommended that investigators should "always try to collect normal control data even where population norms may already exist." These are not intended to replace the controls, but rather are to allow recognition of systematic differences from the controls. The average stature and appearing individuals with MMED served that role in this study and it was the unexpected elevation in their minimal frontal distance (ft-ft) that drew initial attention to the systematic error. The MMED pattern was first confirmed on a first small normal control group (n = 21) and the MMED Z-scores were then subtracted from those of the other dysplasias. This avoided recognizing spurious patterns and missing true profiles which had been obscured. That the ft-ft error was systematic and consistent is further substantiated by the fact that it is also seen in an earlier publication by the author [Hunter and Allanson, 1994]. Measurements obtained by recognized experts in the field may differ significantly, and Ward [1989] reported that the ft-ft norms reported by Farkas [1981] were consistently 2 or more SD above his own and those reported by Krogman [1970]. The normative data for this study were those of Farkas [1981] but were obtained from Dr. Ward who had substituted his own ft-ft norms. The instruments used in this study were identical to those used in studies reported by previous authors [Ward and Bixler, 1987; Ward and Jamison, 1991; Allanson et al., 1993]. The study and control populations were both of mixed European origin but differences in the precise ethnic mixture might account for some variation.

This study would have been improved had the author demonstrated precision and inter-observer comparability by statistically valid standard studies at the outset. Nevertheless, this paper has confirmed that craniofacial anthropometry can identify pattern profiles that are characteristic of some of the more common chondrodysplasias, and in some cases may reveal findings that are not generally appreciated. It has also shown that systematic errors may occur in such studies, and thus emphasizes the admonition of Ward [1989] that a control sample be included so as to allow recognition of such errors. The latter might be further reduced by workshops for those planning to use craniofacial anthropometry, preferably led by recognized experts and those who have established the population controls.

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